

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ANTIVIRAL DRUGS ADVISORY  
COMMITTEE**

**DATE OF MEETING: 01/14/98**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ANTIVIRAL DRUGS ADVISORY  
COMMITTEE**

**DATE OF MEETING: 01/14/98**

**SUMMARY MINUTES**

Food and Drug Administration  
Center for Drug Evaluation and Research

**SUMMARY MINUTES**  
**SUBCOMMITTEE OF THE ANTIVIRAL DRUGS ADVISORY COMMITTEE**  
January 14, 1998  
Quality Suites-Shady Grove, Rockville, MD

Antiviral Drugs Advisory Committee Members  
Henry Masur, MD (Subcommittee Chair)  
Wafaa El-Sadr, MD

SGE Consultants (Voting)  
Susan Cohen, BS  
Bartley P. Griffith, MD  
Lawrence G. Hunsicker, MD  
E. Steve Woodle, MD  
Steven Piantadosi, MD, PhD  
Steve Self, PhD  
Darrell Abernethy, MD, PhD

SGE Consultant (Non-voting)  
Ileana Pina, MD

Guest (Non-voting)  
Randall C. Starling, MD

FDA Participants  
Mark Goldberger, MD, MPH  
Joyce Korvick, MD  
Michael Elashoff, PhD  
Paul Flyer, PhD

These summary minutes for the January 14, 1998 Antiviral Drugs Advisory Committee meeting were approved on 3/5/98

I certify that I attended the January 14, 1998 Antiviral Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired

151

Rhonda W. Stover, RPh  
Executive Secretary

151

Henry Masur, MD  
Subcommittee Chair

Subcommittee of the Antiviral Drugs Advisory Committee Meeting, January 14, 1998

The January 14, 1998 meeting of the Subcommittee of the Antiviral Drugs Advisory Committee consisted of an open session scheduled from 8:00 a.m. to 5:00 p.m.

### **MEETING PROCEEDINGS-OPEN SESSION**

**Topic:** CellCept® (mycophenolate mofetil), Syntex, USA, Incorporated, for immunosuppression following cardiac transplantation.

Approximately 100 persons were in attendance. Background materials provided to committee members included briefing documents from the sponsor and the FDA.

#### **Call to Order**

The meeting was called to order by Dr. Henry Masur, Chair, at 8:11 a.m. The subcommittee and FDA participants introduced themselves.

#### **Conflict of Interest**

The conflict of interest statement was read by Rhonda Stover, RPh, Executive Secretary. Full waivers were granted to Dr. Henry Masur, Dr. Wafaa El-Sadr, and Dr. Steven Piantadosi. These waivers allowed these individuals to participate in the committee discussion with voting privileges. A limited waiver was granted to Dr. Ileana Pina. This waiver allowed her to participate in the committee discussion with no voting privileges.

#### **Introduction**

Dr. Mark Goldberger, Director, Division of Special Pathogen and Immunologic Drug Products, FDA, gave brief introductory remarks. He expressed appreciation for the magnitude of the sponsor's study and for the subcommittee's level of expertise.

#### **Sponsor Presentation**

After the introduction by Dr. Mary Jean Stempien, Dr. Richard D. Mamelok presented data from the primary efficacy study, MYCS 1864. This study was the first double-blind, randomized controlled trial of an immunosuppressant in cardiac transplantation. The study's objective was to compare the efficacy and safety of CellCept with azathioprine, each in combination with cyclosporine and corticosteroids.

Dr. Mamelok discussed CellCept's efficacy by reviewing MYCS 1864's design, analysis, and outcomes. He gave the rationale for the use of azathioprine as the control and for the selection of co-primary endpoints. Dr. Mamelok stated that the choice of a primary endpoint was difficult because the detection and quantification of rejection in cardiac transplantation is imperfect and evolving. The study's co-primary endpoints were (1)

death or retransplantation (survival) with the hypothesis that CellCept was equivalent to azathioprine at 1 year post transplant and (2) biopsy-proven rejection with hemodynamic compromise with the hypothesis that CellCept is superior to azathioprine at 6 months post transplant. Dr. Mamelok presented data from the treated population for these endpoints as well as other secondary rejection endpoints that supported Cellcept's efficacy claims.

Dr. Mamelok reviewed CellCept's safety profile. Based on renal transplant studies and the MYCS 1864 study, it was concluded that relative to azathioprine, the safety profile of CellCept 3grams in cardiac transplant is similar to the safety profile of CellCept 2 grams and 3grams in renal transplant. However, H. simplex and H. zoster infections are more common in cardiac transplant.

Dr. Leslie Miller provided a clinical perspective of the MYCS 1864 study data. He reviewed the status of immunosuppression and rejection in heart transplantation and discussed the importance of the study's rejection and survival findings to the clinician. Dr. Miller commented on the difficulty in assessing rejection and the use of triple therapy as the international treatment standard. Dr. Miller stated that this study was an advancement for the field of heart transplantation because it established new criteria for defining hemodynamic compromise, caring for patients, and initiating rejection therapy.

Dr. Stempien provided the closing remarks for the sponsor's presentation. She reviewed the study's design challenges and efficacy claims. Dr. Stempien stated that CellCept is efficacious in preventing cardiac rejection and death and that there is evidence to suggest the superiority of CellCept over azathioprine. She also commented that the treated population analysis was appropriate and scientifically valid.

#### FDA Presentation

Dr. Joyce Korvick introduced the FDA's presentation and commented on the MYCS 1864 study design. Dr. Michael Elashoff gave the FDA's statistical presentation of CellCept's efficacy analysis. Dr. Elashoff discussed the study's intent-to-treat and treated populations and compared them in an analysis of the study's endpoints. He stated that although the treated analysis is a clinically relevant analysis, concern exists about the sponsor's emphasis of this more favorable data after the study was unblinded and analyzed.

Dr. Elashoff further highlighted the disparities between the protocol and the analyses that the sponsor presented. He stated that the intent-to-treat analysis should be viewed as the primary analysis, and that the p-values in the treated analysis should be adjusted to reflect the multiple comparisons. Dr. Elashoff also gave an example of equivalence methodology for the survival endpoint.

Dr. Elashoff discussed the results of the adjusted analyses for the rejection and survival endpoint data. The analysis of the rejection endpoints indicated that (1) no planned rejection endpoint was significant, (2) no unplanned rejection endpoint was significant

after multiple comparison adjustment, (3) CellCept had a small numerical advantage for most definitions of rejection and (4) the endpoints are overlapping. Dr. Elashoff explained that none of the rejection endpoints demonstrated superiority on its own. Additionally, Dr. Elashoff reviewed azathioprine's efficacy and its potential impact on the equivalence claim for the rejection endpoint since azathioprine has not been shown to be effective for six month rejection. The analysis of the survival endpoints indicated Cellcept's equivalence for the intent-to-treat and treated analyses.

Dr. Joyce Korvick concluded the FDA presentation with a review of CellCept's safety and a summary of the FDA's efficacy findings. She stated that CellCept's safety profile is similar to that seen in renal studies specifically comparable to the 3 gram dose. Dr. Korvick also stated that CellCept is similar to azathioprine for the prevention of biopsy-proven rejection or death at six months and that CellCept is at least as good as azathioprine for the prevention of death or retransplantation at one year.

### Open Public Hearing

There were no open public hearing speakers.

### QUESTIONS TO THE COMMITTEE

(Total votes=9)

- (1) Is CellCept safe and effective for the prevention of organ rejection in cardiac allograft patients?

Yes=9

No=0

Additionally, the majority of the subcommittee stressed that the evaluated data indicates CellCept's equivalence to azathioprine and that it does not indicate Cellcept's superiority to azathioprine.

- (2) Please comment on the design of future cardiac transplant studies, including the choice of control and 6-month endpoints.

The subcommittee discussed many aspects of cardiac transplant trial designs such as randomization, initiation and duration of therapy, endpoints, statistical methods, and rejection diagnosis. The control using azathioprine as part of a three agent arm was regarded as practical and in line with current standards of care. However, the clinical efficacy of azathioprine must be explored further. The need for the evaluation of endpoints at intervals  $\geq 6$  months was expressed with an emphasis on long-term followup.

The meeting was adjourned at 2:23 p.m.